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Original Articles

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RECENT ADVANCES IN THE MEDICAL TREATMENT OF HEART DISEASES*

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ONE HUNDRED years ago today on the 11th of February, 1847, Ellen Bouse, aged 34, entered the Massachusetts General Hospital under the care of Jacob Bigelow, then aged 60, and Oliver Wendell Holmes, then aged 38, because of severe pain and swelling of both ankles, both knees, both shoulders, and both wrists beginning one week earlier. Her skin was hot and her pulse rate was 120. Magnesium sulphate, elixir of opium, and fomentations of the painful joints were prescribed but she showed little improvement in the weeks that followed; in fact in some respects she grew steadily worse, with the development of nausea and vomiting and a "bellows murmur" coming with the first heart sound. As this murmur grew louder tincture of digitalis was given at a dose of 8 drops increasing to 15 drops every four hours except when there was vomiting or diarrhea. Other medicines and therapeutic measures included senna, aloes, colocynth, castor oil, jalap, rhubarb, soapsuds enemas, mercury, sodium and potassium tartrate, peppermint, cinnamon,

* Read before the New York Heart Association at The New York Academy of Medicine, February 11, 1947.

aconite, castoreum, spirits of nitrous ether, wine of colchicum, camphor inside and out, sinapisms to epigastrium and joints, blisters to the precordium and nape of the neck, and leeches to the temples and over the heart. Slowly she sank into a decline complicated by severe psychosis and on the 29th day of April she was discharged, in despair, I judge, by O.W.H. to the Insane Asylum, I presume McLean.

Twenty-five years ago on the 4th day of February, 1922, Helen McCarthy, 23 years old, entered the Massachusetts General Hospital because of dyspnea, palpitation, weakness, and swelling of the ankles without pain. Her initial diagnosis was auricular fibrillation, myocardial insufficiency, and right hydrothorax. Fourteen years earlier at the age of nine she had suffered an attack of severe chorea and one and one half years before admission constant palpitation set in. Seven weeks ago she grew much worse with dyspnea and moderate edema but treatment by rest and digitalis was followed by considerable improvement. Yesterday she suddenly became orthopneic and faint and was referred to the hospital. At entrance she was found to be slightly cyanotic with engorged neck veins, right hydrothorax, enlarged tender liver, edema of the ankles, and a much enlarged heart with systolic and diastolic murmurs, not otherwise described. The heart rate was irregular at 118 and the blood pressure was 110 systolic and 80 diastolic. She remained in the hospital four weeks with a fluctuating course but mostly down hill. There were three distinct febrile episodes lasting a few days at a time with leukocytosis, pleural pain, and X-ray evidence of pulmonary consolidation, called bronchopneumonia, as well as of pleural fluid. Blood cultures yielded no growth. Treatment consisted of chest tapping thrice, digitalization in full, morphine, codeine, acetphenetidin, triple bromides, veronal, neoarsphenamine twice because of the discovery of a positive Wassermann reaction, soft solid diet, and limited fluid intake. No diuretic therapy per se was prescribed and no diagnosis of probable recurrent pulmonary infarction or active rheumatism was suggested. On March 5th she was discharged it was said somewhat "relieved," but died at home four days later.

It is evident from these two case reports that considerable advance has been made during the last century and even during the last twenty-five years in the medical treatment of heart disease, but it has been slow and laborious. There is little or nothing of the spectacular growth and dramatic effects belonging to cardiovascular surgery about which Rob-

ert Gross, one of the ablest pioneers in the field, has just told us. Worthwhile advances have, to be sure, been made in the understanding of heart disease and much ground work has been laid but the greatest advances in medical treatment of the causes of heart disease are still to come. God willing and with the world at peace they are very likely to arrive, at least some of those of major importance, within the next twenty-five years. I only hope that I may myself live long enough to see them—it will be a great day for us all, since the major causes of death, before old age comes, are still the cardiovascular diseases, in particular, the rheumatic, the hypertensive, and the coronary.

One of your own great leaders in New York, to whose name I would like to pay tribute, John Wyckoff, was one of the very first to follow the lead of Richard Cabot in pointing out the fundamental importance of classifying cardiac diagnosis by etiology as well as by structural change and functional condition. Simultaneously in New York and Boston the classification of heart disease which has now become "classical" was worked out and, simple though it is, has proved, I believe, to be the most important step made clinically in the management of heart disease. It has for over two decades now called attention to the preponderant need of treating and preventing the causes of heart disease rather than of concentrating on the therapy of damage already done and of the disorders of function arising therefrom wherein, as a matter of fact, our chief medical advances in recent years have actually been made.

We are thus only at the threshold of a new era of advances in the study of the causes of heart disease and of their treatment. We have progressed to the point where we do know what we need to learn. We also have the obligation to tell the public of our ignorance and yet at the same time of our hope that with their support we may forge ahead. Some things we have learned which can be applied at once through community effort but we must take care at the same time not to delude ourselves and others with false enthusiasm based on the frequency of heart diseases alone and on the idea that we can at once institute a campaign to control them all. We must take the people into our confidence and tell them how little we actually know about the chief causes of heart disease though at the same time we should urge their *patient support* of our future efforts, particularly in fundamental clinical and laboratory research. Fortunately the lay public is already interested and

sympathetic and is awaiting word from us about what to do. Also fortunately there are active associations of doctors and laymen of experience and wisdom who, after years of solid work of organization and study, are now ready to lead the way. The first major heart association in this country was organized right here in New York in 1915 and was called the Association for the Prevention and Relief of Heart Disease. Other pioneer groups were formed in Boston, Philadelphia, Chicago, and San Francisco. In 1924 members of these local groups met in St. Louis and organized the American Heart Association which is now the parent body with wide interests and new and extensive plans for the national coördination of all or almost all the groups and individuals at work on this great menace to the health of the nation. It is fitting that this meeting tonight to help inaugurate the new drive against heart disease should be held here in New York City which is both the home of the oldest local heart committee and the headquarters of the national association itself. I appreciate the honor and the significance of the occasion.

Now let me review briefly some of the recent medical advances in the treatment of heart diseases and follow that with the more important observations on what is still to be done. Let us start with the structural changes which until our generation constituted the great bulk of what was known and of what was discussed in the textbooks of the day: valvular and vascular deformities, cardiac enlargement, and pericarditis. We have made feeble advances medically in this area; surgery has done far better, in fact it is in this very field that surgical therapy has achieved brilliant results in the correction of congenital or acquired vascular anomalies, in the reduction of hypertensive cardiac enlargement by lumbodorsal sympathectomy, in the drainage of pericardial sepsis, and in the resection of constricting pericardium.

Medically we can do nothing to correct deformed valves or blood vessels although so-called functional or relative valvular insufficiencies can on frequent occasions be cleared by improving myocardial tone in the course of treating heart failure by digitalis and otherwise. At this point I would like to interpolate the story of a patient who has shown us what an important role natural recovery may play in the clearing up of signs of heart disease, that is, in its reversibility. A lad 14 years old was seen and followed for rheumatic heart disease in the Children's Heart Clinic of the Out Patient Department of the Massachusetts Gen-

eral Hospital 23 years ago. He had had rheumatic fever, his heart was somewhat enlarged, and he showed typical mitral systolic and diastolic murmurs. The latter murmur was so pronounced that none of us (and several experienced cardiologists were involved) had any hesitation in diagnosing considerable mitral stenosis. This was the period when mitral valvulotomy was being carried out in a series of patients in Boston. Because of the threat of the future and of the apparent suitability of this patient for the operation it was agreed by all concerned that it should be carried out. Accordingly a date was set but an acute upper respiratory infection caused postponement. The boy was sent home to wait but never returned for the operation. Although he was followed up in a desultory way in the years succeeding, the full significance of the lesson he taught us did not attract our attention until about three years ago when at the age of 34 years, twenty years afer our original study of him, this patient entered my general medical ward at the Massachusetts General Hospital with pneumonia. He quickly convalesced under chemotherapy and before discharge was appraised for slight (grade 1) apical systolic and diastolic murmurs without any cardiac enlargement at all. It then turned out that he was the same patient who had been diagnosed as having pronounced mitral stenosis 20 years earlier. What had happened was then clear as the result of other, though less striking, lessons which we had learned in the intervening 20 years. At the time of our first examination this boy had been suffering from active rheumatic myocarditis unrecognized by us and had a dilated left ventricle responsible for most if not all of the mitral murmurs heard at that time. Slowly the activity of the rheumatism subsided and with it the cardiac enlargement and murmurs; it is probable that the slight mitral systolic and diastolic murmurs that were found 20 years later were due to minimal residual deformity of the mitral valve which need cause neither disability nor shortening of life if further rheumatic fever can be escaped.

The one other type of heart disease that much more frequently and dramatically can reverse itself is that due to coronary artery narrowing or occlusion; here no matter as a rule what therapy we apply, aside from common sense measures and patient waiting, a large proportion of cases improve or even recover entirely through the development of an adequate collateral coronary circulation or the healing of myocardial infarcts. This possibility of spontaneous recovery from rheumatic and

coronary heart disease must ever be borne in our minds lest we delude ourselves into overconfidence as to the effect of various drugs and other therapeutic measures; on the other hand, it should not discourage or prevent us from constantly seeking better and more specific treatment.

That part of cardiac enlargement composed of dilatation, which so often is the chief reason for increase in heart volume, can often be lessened by medical treatment of which more anon. The same is true in some cases of hypertensive cardiac enlargement by either surgical or dietary treatment of the hypertension or quite likely by prolonged rest; possibly even the heart weight may be reduced by a decrease of the hypertrophy itself but of that we have no proof.

The medical treatment of acute bacterial pericarditis has of recent years advanced a good deal through the introduction of chemotherapy; even tuberculous pericarditis may thus, we hope, be some day controllable. With such specific treatment of the acute and subacute infections of the pericardium, chronic constrictive pericarditis should, in the course of time, become more and more of a rarity. What I have just said about bacterial pericarditis applies also to acute and subacute bacterial endocarditis which now can be stopped in the considerable majority of cases by chemotherapy before the valves, already deformed congenitally or by rheumatism, are further damaged.

From these small triumphs of the medical treatment of structural changes in the heart let us see what has been accomplished in the medical treatment of disorders of cardiac function, brought into the limelight a generation ago by Mackenzie, Wenckebach, and various other leaders in the study and treatment of heart disease. Myocardial weakness and failure have been handled more and more effectively with each passing decade, but the progress has not been rapid enough to be dramatic. In the first place 25 or 30 years ago there was a return to William Withering's excellent advice about digitalization so clearly presented in 1785. At the same time or soon thereafter came the important recognition of the great value of the maintenance of the full digitalis effect by the giving of daily rations. I can well recall the beneficent change resulting from this soon after my hospital interne days—we no longer saw the numerous cases of acute heart failure enter the emergency ward because of the wearing off of the effects of the customary so-called course of digitalis given a month or two earlier. A further advance that has come slowly in this country is less dramatic but in the

long run, I believe, sound, namely the introduction for routine use of the purer preparations of digitalis, the glycosides such as digitoxin which can be used directly by weight without the bother and uncertainty of animal standardization.

Next in the line of advances in the medical treatment of myocardial failure in our time was the improvement of diuretic therapy. Mercury had, to be sure, been used by mouth for generations as a vigorous diuretic but the refinement of the mercurials that can be given by vein or intramuscularly was certainly a step ahead, supported by acid producing or sodium extracting salts like ammonium chloride by mouth. At first such therapy was often limited to cases of obvious dropsy, but quickly it was realized that even left ventricular failure with dyspnea in attacks or on effort with or without evident pulmonary edema can be greatly benefited by occasional doses of mercurials or by the constant use of ammonium chloride. There are two bits of advice about diuretic therapy that in passing I would like to interpolate. In the first place, small doses of the mercurials may suffice to produce adequate diuresis without causing extensive dehydration or exhaustion—quite often I have found that ½ cc. of mercuhydrin or mercupurin is better than the 2 cc. customarily given. In the second place, it should be remembered that it is possible to go rapidly from the frying pan into the fire, that is, from the one extreme of dropsy to the other extreme of dehydration with sodium depletion and even death. Too abrupt a change in body chemistry is doubtless unwise. I remember to have seen such a change thirty years ago after too vigorous a diuresis with mercury by mouth; and I have seen the same thing happen only thirty days ago after mercury by vein.

A third important advance in the medical treatment of congestive heart failure has been long in the making but only recently has it come into general use. That is the low sodium diet. Some salt restriction had been advised and practiced for many years but merely half heartedly. It was only when it became recognized that every single fraction of a gram of sodium chloride ingested in twenty-four hours might make the difference between success and failure, and that the amount of water ingested didn't matter at all (except that it should be adequate rather than limited) that a new and happier regime for the water or rather brine-logged patient began. He now could do with less of the troublesome mercurial injections, he was no longer thirsty, and he

could often increase his activity. To be sure a sodium chloride intake limited to 1.5 grams daily renders a diet unpalatable but it can be tolerated for a little while until such restriction is no longer necessary. As in the case of mercurial diuresis, so here too, especially when mercurials and the low sodium intake are combined, there can be too much of a good thing.

The last few paragraphs present some of the soundest and most commonly used medical measures introduced in recent years in the treatment of heart disease but they are after all desperate measures, that is, treatment directed to the end results of heart disease. They are, of course, essential and do prolong life somewhat and at the same time do render the last days or months or years more comfortable. No longer do patients die in the distressing dropsical states that I can in my earlier years so well remember; some complication now, like pulmonary embolism or infection, is likely to end the tale. Any boast, however, of our ability to render the last days of our cardiac patients more comfortable and more numerous is in feeble contrast to our inability to prevent or to stop the diseases that so seriously affect the heart. To those I shall shortly come.

The other common disorders of function against which we have advanced in our medical treatment are the arrhythmias. Mackenzie had only digitalis for auricular fibrillation and flutter and bromides for extrasystoles and paroxysmal tachycardia. Quinidine came into use after the first World War and is still commonly employed with effective results by many physicians who are familiar with it. During the shortage of the commercial drug made from the Javan cinchona bark during the second World War a synthetic quinidine was made from quinine and this has been shown to be as effective as the commercial quinidine. The efficient use of digitalis remains, however, the drug of choice in many cases of auricular fibrillation and flutter, not to restore normal rhythm but to reduce the ventricular rate to a reasonable level. For long or exhausting paroxysms of regular auricular tachycardia the cholin derivative mecholyl has frequently been effective through its vagal effect, the excess of which can be avoided by the emergency use of atropine. For the Adams-Stokes syndrome, epinephrine parenterally, introduced by Parkinson, remains the drug par excellence though some effects can be obtained by the use of ephedrine, paredrine or even on occasion, atropine.

Now we come to the real problem, namely, that of the treatment and prevention of the underlying causes of heart disease. If we include every factor which affects the heart harmfully at all, the causes of heart disease would be legion, but there are really only a few that are responsible for the very great percentage (95 per cent or more) of clinically important cases of heart disease; it is in our present discussion quite unnecessary even to list the numerous conditions like mumps or influenza which can in very rare cases seriously involve the heart. The important causes of heart disease are congenital deformities, rheumatic fever, bacterial endocarditis, diphtheria, syphilis, hypertension, and coronary arteriosclerosis. Two of these are certainly on the decline, diphtheria and syphilis, in large part, of course, because of their early recognition and increasingly more adequate treatment. In fact the former is almost, though not quite, nonexistent; it flared up a bit in the recent war because of the late treatment of some cases of skin diphtheria. The latter, syphilitic aortitis, has become not only much reduced in communities where syphilis itself is under better control, but after it has become evident in middle age it is now generally agreed that active though careful antisyphilitic treatment holds it in check and in some cases even seems to cure it.

I have not listed thyrocardiac disease at all, for during the last decade it has become almost extinct, at least in communities where thyroid disease is early recognized and adequately treated by surgery or otherwise. I see about one new case a year now, usually in an elderly woman who has suffered for years from a rather low grade chronically active but unrecognized thyrotoxicosis. Twenty odd years ago serious thyrocardiac disease was not rare with its auricular fibrillation and cardiac enlargement and failure. It was in that group of cases that Lahey and Hamilton made history in the demonstration of the reversibility of heart disease by surgery consisting of subtotal thyroidectomy.

A few words should be said about the problem of congenital heart disease. It is obvious that medically we can do nothing about it in the baby or young child in whom it is recognized, but there are some indications that we may be on the threshold of its prevention, in some cases at least. Gregg and Swan of Australia a few years ago reported the finding of multiple congenital defects, including cardiovascular anomalies, in infants born of mothers who suffered German measles during the first two months of pregnancy. We have ourselves encoun-

tered such cases but the complete story of how great the hazard is and about the effect of other virus diseases in early pregnancy has not yet been told. Prevention or early treatment of such diseases, if their incrimination is proved, may be the first important medical advance in this field, which at present remains almost entirely a problem for the surgeon.

Let us turn now to the brightest spot of all in the advance of the medical treatment of heart diseases in the last few years, namely the chemotherapy of bacterial endocarditis. Undoubtedly a good many instances of the acute variety are now prevented or early cleared by stopping the general infections, pneumococcic, gonococcic, streptococcic, or staphylococcic, that were once responsible for the great majority of cases of acute bacterial endocarditis. The treatment of the subacute variety of bacterial endocarditis, always more important clinically than the acute type, has undergone a dramatic change within our recent memory. About eight years ago the sulfonamides with much struggling reduced the mortality from Streptococcus viridans endocarditis from practically 100 per cent to about 94 per cent. This was a step ahead certainly and a forecast of a more hopeful future, but most of the patients still died. When penicillin entered the picture our spirits rose at first only to be dashed by the pessimistic early official report of the apparent failure of the drug in 17 patients. Soon thereafter there appeared the encouraging paper by Loewe which pointed the way to the dramatic success that followed. He showed that if enough of the drug is given the majority of cases of subacute bacterial endocarditis can be cured. The principle behind the success of this treatment is simple enough but it is often overlooked. It was behind the success both of liver treatment of pernicious anemia and of lumbodorsal sympathectomy for hypertension; the increase of the amount of treatment accounted for the success of each. Another lesson that we may derive from these experiences is that we must be constantly on the watch for individual accomplishments outside the rule of routine therapy; no matter if they seem at variance at first they may be proved of value by time and further trial. Now that international medical communications are again opening up after the second World War it is our duty to stimulate the exchange of information about diseases and their treatment throughout the world. There are many important things for us to learn about heart disease and its causes in every corner of the world. Is

hypertension, for example, really as rare in China as rumor has it? And if so, why?

Finally we have arrived at the crux of our problem, namely the medical treatment and prevention of the three commonest kinds of heart disease, the rheumatic, the hypertensive, and the coronary. If we can develop really adequate therapeutic measures against these three major causes of death we shall have succeeded in our aim today. But what can we actually do now? Truly very little. It is here in the most important aspect of our campaign against heart disease that we need the sympathy and the support of the lay public the world over. We need not only community planning but also support of studies of all kinds concerning these three major problems. We may somewhat empirically though effectively develop therapy to influence these vital factors, such as lumbodorsal sympathectomy for hypertension, but we must go deeper than that. We must get at the roots and then work more directly with our eyes open. Clues may be anywhere and therefore many different researches should be supported, both clinical and laboratory, and preferably the two combined in the best fashion of clinical investigation.

Fortunately the battle is well joined or at least started with respect to rheumatic heart disease. The soundly established Council on Rheumatic Fever has been backed by all the organizations and groups in the country especially experienced and interested in the subject. Its aims are manifold: to stimulate research, to coördinate existing knowledge, and to apply what is already known. It is has been a long hard uphill fight but the active interest of many investigators in the future promises much. We are on the edge of answers to many questions. For example, what is the exact relationship of rheumatic fever to the hemolytic streptococcus infection which so often precedes by ten or twelve days the onset of rheumatism? Can we prevent rheumatic fever by preventing hemolytic streptococcus infections? If so, will chemotherapy or other measures of prevention or early treatment do the trick? What role does familial susceptibility play? Can rheumatic fever itself be checked in the future after it begins by something more effective than the salicylates? Positive answers to such questions as these will reduce or wipe out the chief cause of death in the second decade of life and the major cause of disability in young adults.

What now about hypertensive heart disease and the hypertension that causes it? One of the most dramatic experiences of my lifetime

has been my observation of the control of hypertensive heart diseases, which in some cases had progressed to the stage of actual failure of the left ventricle, by Smithwick's lumbodorsal sympathectomy. I assure you that this has not been an optical illusion on my part, for during the previous twenty years or more I had utilized the current medical therapy of the day with negligible or at best only palliative results *after the stage of serious hypertensive heart disease had developed.* Rest, restricted diets, and drugs such as the nitrites, sedatives, and thiocyanates had helped temporarily, though I had not, to be sure, employed the stricter low salt and rice diets which have shown of late on occasion a helpful effect, at least for the time being. But here in lumbodorsal sympathectomy was something which as a sceptic I encountered five years ago that did a different thing; in a large percentage of younger cases with adequate blood pressure reactions and renal function, good results, lasting for several years, have been attained whether or not the myocardium showed evidence of severe strain—in fact, other things being equal, the myocardial fatigue itself has been, in my experience, an indication rather than a contraindication, as in the old days, for the operation of lumbodorsal sympathectomy. But effective as it has often proved, surgical treatment of hypertension seems to me to be but a temporary makeshift; it is a difficult, painful, and tiresome, though in experienced hands, not a hazardous procedure. We must have something better eventually, both in prevention and in treatment, based on the as yet unknown causes of hypertension. Some drug, some diet, or some other simple measure, physiologically sound, will be the final answer. To date no long enough lasting adequate medical measure has, so far as I know, been discovered.

Last, but not least, in the catalogue of heart diseases and the one that most dramatically ends the lives of many important persons in the world at the very peaks of their useful careers, is coronary heart diseases. Like the rheumatic fever problem, so too both the hypertensive and the coronary problems deserve outstanding attention, even perhaps a formation of national councils for concentrated and coördinated work thereon, similar to that established for rheumatic fever. The crippling and often fatal effect of obstruction to the coronary blood flow by excessive atherosclerosis and intimal thickening is well recognized and its preponderance in the male sex in middle age and earlier is well known. Ten years ago Glendy, Levine, and I found that the ratio of males

to females with coronary heart disease under the age of 40 years was as overwhelming as 24 to 1. Here has been the most obviously neglected clue. We are studying now the anthropometric and metabolic findings in young "coronary" cases. Dock has pointed out the thicker coronary intima in newborn males as compared with newborn females. But we have just scratched the surface. We must learn much more and then apply scientific measures of prevention and early treatment to check the appalling waste of lives of useful persons. At present all we can do medically is to wait patiently with the help of restricted activity and the use of nitrites for the development of an adequate collateral coronary circulation or for the healing of a myocardial infarct. Most drugs and other measures of treatment that have been recommended in the past have not proved their worth, and surgery for the end stages of coronary heart disease hardly seems promising—we must begin at the other end. Every method of study of this vital problem the world over should be utilized including the geographic, racial and economic distribution of the disease. The life insurance companies in particular should take a leading part but the problem concerns us all, doctors and laymen alike. Whoever has a desire to aid in these important researches need but say so to any of us who are engaged therein, and such aid may be just the last bit needed to lead to a vital answer.

In closing, let me leave with you my firm conviction of the great value of the development of the community and national efforts about to be inaugurated in our struggle against heart disease, but at the same time let me emphasize our great ignorance of the causes and adequate treatment and prevention of all three of the major causes of heart disease; rheumatic fever, high blood pressure, and coronary artery obstruction. It is against these three foes of man that we must bend our greatest efforts.

CARCINOMA OF THE PROSTATE*

ARCHIE L. DEAN

Attending Surgeon, Memorial Hospital

WHEN Engelbach in 1888 collected 114 reported cases of malignant tumors of the prostate he did much to clarify the problem of obstruction of the bladder outlet. Even so, it was not before almost a quarter of a century had passed before clear cut differential diagnoses were generally made between benign and malignant prostatic diseases. Even though significant progress was being made, how primitive such a period now appears. Although our successors, principally because of greater knowledge of the steroid hormones, will be in a position to pity our floundering efforts to solve the problem, it is a fact that during the life of every experienced urologist now practicing, prostatic cancers and their proper treatment have become exceedingly important.

These tumors are not rare. It is recognized that of every 100 men who reach the age of sixty years, five will develop prostate cancers. In addition, careful microscopic studies of large numbers of prostates removed because of benign hyperplasia have shown unsuspected nests of cancer cells in approximately 20 per cent. Many ingenious methods of treating these tumors have been devised and skillfully performed; radical operations have been perfected by which not only the entire gland and its capsule but also the seminal vesicles and bladder trigone may be removed; radon and radium implants have been inserted in and about the tumor through the intact perineum, through the perineum with the tumor exposed and suprapubically through the opened bladder; roentgen therapy has been delivered by increasingly powerful units, but in spite of all efforts a cure was rarely achieved.

Surgery failed principally because prostatic cancers grow for a long time without causing any symptoms. When the tumor begins to obstruct the bladder and local symptoms insidiously develop, the disease, with few exceptions, has extended beyond reach of the most radical

* From the Department of Urology, the Memorial Hospital, New York.
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operation. Interstitial radiation, while sufficiently powerful to destroy the tumor in areas closely adjacent to the embedded seeds or needles, failed because of technical difficulties in placing the implants accurately throughout the entire growth. External radiation was unsuccessful because of the radioresistance of adenocarcinomas, the considerable distances of the prostate from the nearest body surfaces and the limitations placed on the method through fear of injuring the bladder or rectum. To illustrate the poor results produced by these methods even when carefully conducted, and to establish a basis of comparison with the results obtained by newer therapy, the statistics of the University of Michigan Hospital are of great interest.

TABLE I

From University of Michigan Hospital

END RESULTS OF 795 CASES OF PROSTATIC CANCER TREATED FROM 1925 TO 1940

Number of patients followed	783
Patients known to be dead	737
Patients now living	46

Nesbit and his associates[1] studied the end results of 795 cases of prostatic carcinoma treated between the years 1925 and 1940 inclusive. They were able to follow accurately 98.5 per cent of all the patients in the group. As shown in Tables I and II, of the 795 men, 737 have died, 605 of prostatic cancers, sixty following operations, and sixty-seven of other known causes. Five patients died of unknown causes.

TABLE II

From University of Michigan Hospital

CAUSE OF DEATH OF 783 PATIENTS WITH PROSTATIC CANCERS BEFORE ENDOCRINE THERAPY

Cancer of prostate	605
Operations	60
Other known causes	67
Unknown causes	5

Although 132 patients did not die primarily of prostatic cancers there is no reason to doubt but that they died with prostatic cancers and would have succumbed to this disease had no intercurrent illness supervened.

Against such a background of well deserved pessimism the announcement of Huggins[2] in 1941 was startling indeed. This investigator reported that men with advanced prostatic cancers could be benefited greatly by the simple operation of castration. Huggins' clinical work was based on a long series of ingenious animal experiments.[3] Dogs' prostates were isolated from their bladders and a study was made of the normal excretion of prostatic fluid. It was then demonstrated that the administration of androgens stimulated prostatic activity and increased the flow of prostatic fluid. It was shown also that the administration of estrogens promptly stopped the production of prostatic fluid. It was learned that the administration of androgens caused hyperplasia of the epithelial cells of the prostate and that, in some cases, metaplasia became so pronounced that the appearance of the gland simulated cancer. When estrogens were given, these glands promptly returned to normal. Huggins also showed that after surgical castration prostate secretion stopped and metaplasia of the epithelial cells regressed. Although this work was by far the most complete and authoritative on the hormonal relationships of the prostate, earlier investigators had made a number of interesting observations.

Harvey observed that when the hedgehog hibernates the testes atrophy and the prostate also becomes smaller. He observed also that the prostates of bulls became smaller after castration. In 1893, White,[4] on the basis of animal experiments, stated that the castration of dogs "was followed invariably and promptly by atrophy, first of glandular and then of muscular elements, of the prostate." Two years later the same clinician[5] reported generally favorable results in a group of 111 patients castrated by him and others because of prostatic enlargement. In 1898, results were reported following the castration of a number of women for cancers of the breast. Although this treatment of breast cancer never proved successful, it did stimulate further the treatment of prostatic tumors by modification of the endocrines.

After a few years the treatment of prostatic enlargement by castration was largely abandoned. This was probably due to a number of factors. The majority of patients who visited physicians because of

bladder obstruction perhaps required relief more promptly than could be brought about by the removal of the testes; careful pathological differentiation between benign and malignant enlargements of the gland was not performed routinely; and finally, at this time there was greatly increased interest in the development of surgical methods for the relief of prostatic obstruction. For these reasons and perhaps others it was years before further attempts were made to control prostatic enlargement by endocrine methods. Beginning in 1934, Randall castrated five men who had prostatic cancers. Since it was necessary to relieve obstruction in each of these patients, transurethral resections of the bladder outlet were performed as well. Each of these patients followed a course which appeared to Randall to be what one would expect after transurethral resection alone. Therefore he did not report these operations until 1942. At about the time Randall's work was performed, or shortly later, Munger[6] irradiated the testes of a number of men with prostatic cancers for the purpose of castrating them. He noted that these patients did better than his other patients treated by different methods. A number of competent urologists examined Munger's patients at various intervals after treatment and could palpate no evidence of prostatic carcinoma. Beginning about 1938, a number of investigators began to treat patients with prostatic carcinomas by administering female sex hormones by mouth and by pellets of estrogens inserted beneath the skin.

Another important phase of our subject is the remarkably rapid progress made in chemical laboratories through which tests were perfected to establish detailed diagnoses not only of the nature of the primary tumor but also of the extent of metastases. These tests were concerned principally in measuring the amount of phosphatases in the serum. Phosphatases are enzymes which split organic phosphates to give free phosphate ion. They fall into two groups according to the hydrogen ion concentration, (pH), at which they are most active. The acid phosphatases usually have a broad maximum of activity between pH 4.0 and 5.5, the alkaline phophatases usually are most active in a narrow range between pH 9.0 and 9.5. Their exact properties depend on the tissue of origin and on the substrate used in measuring their activity. In 1935 Kutscher and Wolbergs[7] isolated from the prostate a phosphatase which had its maximal activity in an acid solution. In 1936 the Gutmans and Sproul[8] discovered that bones, the site of metastases from

carcinoma of the prostate, contained acid phosphatase in addition to the usual and well known alkaline bone phosphatase. In 1938 the Gutmans[9] established the fact that there was but little acid phosphatase in the prostates of infants and that this substance increased greatly at puberty when testicular secretion began. These workers found acid phosphatase in the normal adult prostate, the hyperplastic prostate and the cancerous prostate. In 1938 and 1939 the Gutmans and Robinson showed that the acid phosphatase activities of the sera of many patients with metastasizing carcinoma of the prostate were greatly elevated. More recently, Gomori,[10] through his microphosphatase tests, demonstrated that acid phosphatase was present only in the adult epithelial cells of the gland. This was the first exhibition of a secondary sex characteristic of a chemical nature.

Acid phosphatase occurs in many organs, but, with the exception of the prostate gland, no organ ordinarily contains more than one or two Bodansky units per gram of tissue. In the human adult prostate the acid phosphatase activity is high, reaching several hundred units per gram. The production of this enzyme by the prostate apparently requires androgens for its development and therefore does not occur before puberty. The acid phosphatase activity of prostatic carcinoma tissue is usually of the same order of magnitude as that of the normal prostate although it may be less in highly anaplastic carcinomas. Normal human serum contains small amounts of acid phosphatase. This cannot originate in the prostate since the activities of the sera of normal men are the same as those of the sera of normal women who have no organ which contains large amounts of the enzyme. At present the source of acid phosphatase in normal serum is unknown.

Woodard[11] made an important contribution in showing how often elevations in serum acid phosphatase occurred in patients with cancers of the prostate and in those with other diseases. Of seventy-one patients with cancers of the prostate and demonstrable bone metastases 51 or 72 per cent had elevated serum acid phosphatase. Of fifty-six patients with cancers of the prostate and no demonstrable bone metastases 19, or 34 per cent had elevated serum acid phosphatase. No elevations in the serum acid phosphatase have been found in patients with benign hyperplasia of the prostate nor in patients with cancers originating elsewhere which have invaded the prostate. This work and clinical experience appears to show that the acid phosphatase of cancerous

prostatic tissue does not enter the circulation as long as the capsule of the gland is intact. It may enter the circulation and be demonstrable in the serum as soon as local invasion or distant metastasis occurs and it does so somewhat more readily when metastases are in bone than in soft parts. In a few cases (probably not more than 10 per cent) elevations in serum acid phosphatase never occur even in the presence of extensive disseminated disease. In these cases it is possible that the tumor because of its structure produces little acid phosphatase, but additional autopsy material is necessary to prove this hypothesis.

Woodard[12] also assayed the serum of thirty-four women and 167 men who had osteogenic sarcoma, Paget's disease, jaundice of various types, plasma cell myeloma, lymphoma and other diseases not involving the prostate and failed to find any elevations of acid phosphatase. On the basis of this work she concluded that conspicuous elevation in serum acid phosphatase appears to be pathognomonic of metastasizing carcinoma of the prostate.

Many investigators have shown that alkaline phosphatase occurs in the kidney, intestinal mucosa, bones and some other tissues but only that from bones enters the blood stream in significant amounts. This enzyme is excreted by the liver and if this organ is diseased excretion may be impaired and the level in the serum may rise. Alkaline phosphatase production is increased as an essential part of new bone formation and with this activity there is a corresponding increase of the amount in the serum. Metastases to bone from carcinoma of the prostate, being nearly always osteoplastic, cause an increase of serum alkaline phosphatase in about 90 per cent of patients with metastases demonstrable and in some cases before any symptoms referable to bones have occurred. While unlike acid phosphatase, alkaline phosphatase is not specific for carcinoma of the prostate, in a patient without liver disease a rise in serum alkaline phosphatase warrants a strong suspicion that metastases to bones have taken place.

Because of the accuracy of phosphatase assays in showing the clinical status of patients, four reasonably clear cut groups may be recognized on the basis of these tests:

1) Normal men in whom there is no increase in either the serum acid or alkaline phosphatases.

2) Patients with proved cancers of the prostate and normal amounts

of both serum acid and alkaline phosphatases. In this small but important group one may perform radical surgery with a fair chance that the tumor has not grown beyond the gland.

3) A group consisting of the great majority of patients with prostatic carcinoma in whom the tumor has grown through the gland capsule with or without forming demonstrable distant metastases. In our experience the great majority show increased serum acid phophatase.

4) Patients with prostatic cancers which have metastasized to bones. In this group both acid and alkaline phosphatases in the serum are elevated significantly. The amount of alkaline phosphatase in the serum so accurately represents the reaction of the bones to the invasion of prostatic carcinoma that quantitative assays give clinical information regarding the immediate status of the patient not obtained by any other examinations such as roentgenograms. When both acid and alkaline phosphatases enter the serum from bone metastases the source of the acid phosphatase is the tumor in the bone while the alkaline phosphatase comes from the bone surrounding the tumor.

The improvement after castration of most patients with apparently hopelessly far advanced prostatic cancers is one of the most spectacular changes to be observed in clinical medicine.[13, 14] The relief of pain from bone metastases probably is most gratifying and it usually occurs within thirty-six hours. Patients bed ridden for months because movements were agonizing and who had, as a result, developed serious contractures of their limbs may begin relearning to walk by the third or fourth postoperative day. Metabolism improves greatly, appetites often become ravenous so that men have doubled their body weight in a few months. Every laboratory test of fitness shows improved health. Improvement not infrequently is of such a degree that these men return to their usual occupations and may even resume activities in sports. Regression in the size of metastases to soft parts is usually prompt. Perhaps the most striking of these is the disappearance of large masses in the lungs, which has been observed many times. The primary tumor also shrinks after castration but at a variable rate and to a variable degree. In some cases one cannot detect any evidence of tumor by rectal palpation a few months after operation but usually regression is not so complete. If the patient had considerable bladder obstruction with correspondingly great quantities of residual urine transurethral resection of the bladder outlet usually is necessary. Roentgenograms of the skele-

ton taken at regular intervals have shown interesting bone changes but as yet we have difficulty in correlating the patient's clinical state with the bone pictures. We have seen patients, apparently much benefited by castration, in whom bone metastases seemed to be spreading. We have also observed what appeared to be improvement in a metastatic area in one side of the pelvis while, at the same time, an obvious metastasis in the other side became visible and grew. However, there is no doubt but that in some cases bone metastases heal, how frequently we do not know.

The testes removed from our patients grossly were normal. Microscopic study showed in practically all cases moderate tubular atrophy with from slight to considerable interstitial cell hyperplasia.

After enjoying greatly improved health for varying periods the men castrated because of advanced metastatic prostatic cancers begin to relapse and die. Usually the onset of relapse is characterized by a return of bone pains.

While observing the effects of castration on about eighty men another group of nearly 100 have been treated with female sex hormones administered by mouth.[15] We have seen no clinical benefit from castration which has not been produced to as great a degree by estrogen therapy although improvement is not so prompt. Relief of pains from bone metastases which occurs so often within twenty-four hours of castration occurs only after estrogens have been given for from ten to fourteen days. The estrogen now used is ethinyl estradiol with the trade name of estinyl. The usual daily dose consists of two tablets, each of .05 milligram, taken on retiring.

Within a month of beginning estrogen therapy feminization of the patient appears. At first the nipples become tender, then the breasts enlarge. Later fat is deposited about the hips, the external genitalia shrink and finally a mons veneris is formed. The skin of the face assumes a finer texture and often the beard thins but it continues to grow. Libido probably is lost to a greater degree with estrogens than after castration, however, few of these patients were active sexually before treatment was started. Psychic changes are few and usually mild. A slight euphoria perhaps is most common. Maniacal states have been described following castration but there probably was instability before operation and a failure on the part of the physician to soothe and encourage the patient and obtain his consent. I have never had a patient

refuse castration and I have never felt compelled to tell him that he had a cancer.

As after castration, patients treated with estrogens often regain their previous physical capacities and carry on comfortably for variable periods when relapse occurs. In our experience there has been little difference in the length of time before relapse after castration or estrogen therapy. We have been able to give no appreciable relief to patients who relapsed after castration by administering stilbestrol, but since estinyl can be given in greater therapeutic quantities, trials with it are now being made although, as yet, they have not proved conclusive. In the same way, our patients who relapsed after estrogens have not been significantly improved by castration. Nesbit, however, reported a patient who failed to benefit from stilbestrol but who was completely relieved by castration. Such an occurrence must be rare.

Thinking it possible that androgen excretion by the adrenals explained relapses I removed both adrenal glands from three men who had relapsed after both castration and treatment with estrogens. None of these men lived more than four days and no further trials were made. Huggins performed the same operation on four patients with little more success.

It will be noted that the foregoing description of the striking response to castration and estrogens applies specifically to patients with advanced cancers of the prostate with bone metastases. Men with less advanced disease without bone metastases and bone pains do not show such prompt or profound benefit. In fact, Herger and Sauer point out that under apparently adequate estrogen therapy metastases develop in this group and they live no longer than patients reported by Bumpus[16] who were in a similar clinical condition and who received no hormonal treatment.

The changes in the serum acid and alkaline phosphatases following modification of the endocrines are of both theoretical interest and clinical importance. When the serum acid phosphatase is elevated before treatment it usually shows a decided drop within a week of castration or within two to three weeks after the beginning of stilbestrol therapy. A more limited experience with estinyl suggests that the effect is similar to that of stilbestrol but further use of this drug may show slight differences. When the serum acid phosphatase is normal before treatment there is no immediate change after either castration or the ad-

ministration of estrogens. When treatment fails to initiate a prompt drop in the serum acid phosphatase the patient usually experiences no clinical improvement. These laboratory data corroborate the clinical observation of Herger and Sauer mentioned above. The presence or absence, therefore, of a prompt response of the serum acid phosphatase to treatment is of great prognostic value.

When a patient who has shown a drop in serum acid phosphatase with clinical improvement later relapses, the onset of clinical relapse, usually indicated by the return of bone pains, may or may not be accompanied by a significant increase in serum acid phosphatase. Sometimes the return of symptoms is preceded by a rise of acid phosphatase. When such a rise occurs it always indicates renewed activity of the disease. Unfortunately, persistence of normal values of serum acid phosphatase does not give assurance that the disease is under control. Probably discrepancies between the clinical onset of relapse and the time relapse is indicated by elevation of serum acid phosphatase are due to the fact that the most clear cut clinical evidence of relapse is the return of bone pains and this symptom may reappear at different stages in the depreciated conditions of different patients. The phosphatase assay, therefore, should be depended on as being the more accurate.

We have employed acid phosphatase assays in another way which has proved of considerable clinical value. Patients are occasionally seen with extensive inoperable tumors which involve the prostate and adjoining portions of the bladder or rectum. In such cases it is important to learn whether the growth originated in the bladder or rectum and invaded the prostate or whether it was primary in the prostate and later invaded the bladder or rectum because in the latter case great benefit may be obtained from endocrine therapy. Since prostatic cancers, even when they infiltrate other organs, contain comparatively large amounts of acid phosphatase, assays of tissue removed from the bladder with a cystoscope or from the rectum with a proctoscope have given a clear cut answer to the problem and have provided a rational basis for successful treatment in a number of cases.

The serum alkaline phosphatase in patients without bone metastases or liver disease is normal. This is not affected by endocrine treatment. As previously stated, the serum alkaline phosphatase is almost always elevated in patients with bone metastases from cancers of the prostate. In our experience within a month after surgical castration 80 per cent

of these men show a significant additional rise of serum alkaline phosphatase to amounts which sometimes become two to three times the initial quantities. When patients continue to have clinical improvement the serum alkaline phosphatase begins to fall after about three months and it may reach normal levels as the bone lesions become quiescent or heal. If clinical improvement is not sustained assays of this phosphatase usually remain high. When stilbestrol is employed only about one-third of the patients show a rise of serum alkaline phosphatase soon after the beginning of treatment. The remaining patients either show no reasonably prompt change when clinical improvement is lacking, or if the clinical response is good there is a gradual decline to normal values. Thus there appears to be a definite biological difference in the reactions of bone metastases to the two types of endocrine treatment.

Some work was done in the laboratories of the Memorial Hospital to show how the endocrines of patients with prostatic cancers were modified by castration or by the administration of stilbestrol. It will be remembered that Huggins[3] believed, as a result of his experimental work with dogs, that the prostatic epithelium, whether normal or cancerous, was dependent for its growth on the relation of estrogenic to androgenic hormones in the blood. Estrogens demonstrably decreased prostatic secretion and androgens increased it in experimental animals. On this basis, therefore, the man with prostatic cancer was castrated for the purpose of removing the source of his androgens. It has been known for several years that men excrete estrogens in their urine. Since they have no ovaries their adrenals have usually been considered the source of these substances. It was thought that castration would not affect the adrenals and that the estrogens, therefore, would remain the same but that there would be a change in the estrogen-androgen relationship toward comparatively higher estrogen and lower androgen values. The administration of estrogens should also cause a similar shift in hormonal relations.

It was surprising to learn that these predicted theoretical changes were not borne out by our laboratory tests. Twenty-seven patients with prostatic cancers were studied in relation to their output of estrogens and androgens before and after castration. Before operation the estrogens averaged 16.6 mouse units per twenty-four hours and the androgens 6.1 milligrams of androsterone equivalent as determined colorimetrically

by the modification of the Zimmerman metadinitrobenzene reaction. Since a healthy young man excretes 15 to 25 milligrams of androgens in a similar period, it will be noted that our patients showed low 17-ketosteroid excretion. After castration, instead of estrogens remaining the same and androgens diminishing, the estrogens dropped in all but one of 16 patients to about one-half (8.5 mouse units) of the pre-castration level while the androgens remained the same or rose slightly (from an average of 6.1 to 7.1 milligrams in the 17 patients tested).

Gonadotropic hormones from the anterior pituitary gland were measured before and after operation in 16 patients. Of these, there was a definite post-castration rise in 11, while 5 showed quantities of this hormone too small to measure. In no case was there a decrease in gonadotropic hormone in the urine after castration.

Quite different from these reactions were those found by assays on 9 men before and after the administration of stilbestrol. Before treatment the estrogens of these men averaged 18.2 mouse units in twenty-four hours, while after treatment the quantity rose tremendously because a certain amount of the stilbestrol was excreted in the urine. The androgens before treatment averaged 8.9 milligrams of androsterone equivalent in twenty-four hours. After treatment these 17-ketosteroids fell in every case to an average of 5.4 milligrams of androsterone equivalent.

Of six patients in whom the excretion rate of gonadotropic hormone was studied before and after the administration of stilbestrol, in none was there a post-treatment rise.

From the viewpoint of hormones excreted in the urine, therefore, the treatment of prostatic cancer by castration differs greatly from treatment with stilbestrol. Castration seems to cut estrogenic excretion in half, tends to raise 17-ketosteroid excretion and to release the pituitary gland from testicular inhibition so that it puts out its gonadotropic hormone in excessive quantities. Stilbestrol raises the estrogenic excretion rate and decreases both the androgenic excretion rate and the quantity of gonadotropic hormone in the urine. It will be remembered that on the basis of phosphatase assays also bone metastases reacted differently to castration and to stilbestrol.

On the basis of present clinical and laboratory experience, therefore, it appears best to castrate the patient suffering pain from cancer of the prostate with bone metastases because in this way pain is relieved most

promptly. Castration also can be recommended for the patient who lives at a distance and would have no regular medical supervision. I also castrate those patients who I think would discontinue estrogens on becoming comfortable. Radical perineal prostatectomy still has an important place in treating those rare individuals whose prostatic cancers have not extended beyond the bladder neck or seminal vesicles. All other patients can be treated effectively, if they respond at all to endocrine therapy, by estinyl tablets taken by mouth. Two tablets daily of .05 milligram each usually are sufficient. While this drug in this dosage is well tolerated it seems best to have it taken on retiring. I have observed no especial benefit from large doses of estrogens before relapse has occurred, nor has there appeared especial efficiency in combining both castration and estrogen administration. The estinyl tablets should not be enteric coated because it is unnecessary and it prevents one from giving an accurate dose. From one of my patients who took thirty-five enteric coated estrogen tablets, twenty-two were recovered, apparently unchanged from the stool. I have had no personal experience in performing radical perineal prostatectomy on patients who were initially inoperable but who improved after taking estrogens although Scott[17] and Coulston, urologists of great experience and skill favor the procedure. No evidence has, as yet, been produced to indicate that the old belief of "once inoperable, always inoperable" is not true.

If relapse occurs under estrogen therapy, castration should be performed. While I have never observed significant improvement from such treatments, it is possible that at least one man, Nesbit's patient, was so helped. When relapse follows castration, estinyl in doses as large as tolerated is recommended. Since with this drug larger amounts of estrogenic hormone can be given without disabling side effects, its use in this way may have promise. Clinical trial in about twenty cases of castration relapse have appeared favorable but the end results are not known. Removal of both adrenal glands to relieve these otherwise hopeless patients has, as yet, proved impracticable. In an effort to depress the output of gonadotropic hormone put out by the anterior pituitary after castration, because there is evidence that this secretion may stimulate androgen production by the adrenals, high voltage roentgen rays have been delivered to the pituitary gland. No marked or protracted benefit has been observed after treatment by us or others such as Herbst,[18] Herger and Sauer or Angrist and Khoury.

In studying the end results of five years experience in treating prostatic cancers by modification of the endocrines it is necessary to combine the reports of a number of observers because few clinics have treated sufficiently large groups of patients to have statistical significance. After treatment has been given, whether it was castration or the administration of estrogens, about 10 per cent of the men continue an uninterrupted downhill course which ends in death. The remaining patients, for the most part, are spectacularly improved. It is not possible at present to know how long this improvement will be maintained in the average case because a number of the patients treated earliest are still free from evidence of disease. However, about 65 per cent of those initially improved have since relapsed and have died. The average time that relapse occurred was thirteen months after treatment was started. The men who do not relapse within a year appear to have an excellent chance of remaining well considerably longer. While members of this more fortunate minority relapse from time to time, a small number have continued until the present in apparent good health, some with no evidence of disease. How long they can survive and whether they are truly cured is uncertain. One of our patients whose prostatic cancer was diagnosed histologically was treated with stilbestrol. He showed no evidence of tumor activity for four years when he died of coronary occlusion. An autopsy was performed and no gross or microscopic evidence of prostate tumor could be found, although sections were made of the entire prostate region. An occasional cure may therefore be possible.

Although remission of pain alone would justify the endocrine treatment of prostatic cancers the best statistics available show that the survival period of patients has been significantly prolonged as well.

TABLE III

From University of Michigan Hospital

SURVIVAL PERIOD OF 735 PATIENTS WITH PROSTATIC CANCERS BEFORE ENDOCRINE THERAPY

Average survival of entire group 21.2 months extremes 1 month and 15 years.
Average survival of 475 patients without metastases 24 months extremes 1 month and 15 years.
Average survival of 260 patients with metastases 17 months extremes 1 month and 176 months.

We are again indebted to Nesbit and his associates[1] in the University of Michigan Hospital, who, in studying their 795 patients treated without endocrine modification found that the average survival of the entire group was 21.2 months.Four hundred and seventy-five of the patients had no evidence of metastases at the time of diagnosis, and their average survival was nearly 24 months—the extremes being less than one month and 180 months (15 years). Two hundred and sixty patients had metastases at the time of diagnosis. Their average survival was 17 months —the extremes being one month and 176 months.

TABLE IV

From University of Michigan Hospital

COMPARISON OF SURVIVAL PERIOD OF PATIENTS NOT TREATED WITH ENDOCRINES AND THOSE CASTRATED OR GIVEN STILBESTROL

	Control 781 Cases		*Orchiectomy 75*		*Stilbestrol 50*	
Month	*No. Dead*	*% Dead*	*No. Dead*	*% Dead*	*No. Dead*	*% Dead*
6	261	33.4	6	8.	1	2.
12	381	48.8	14	18.6	3	6.
18	483	61.9	22	29.3	10	20.
24	542	69.4	28	37.3	12	24.
30	568	75.	32	42.6		
36	610	78.1	41	54.4		
42	637	81.5	46	61.3		
48	648	82.9	50	66.6		

Compared with this large group are two closed series of cases under endocrine treatment which are being followed until the death of the last survivor. One series of seventy-five patients had surgical castration while the other, of fifty patients received stilbestrol by mouth. Table IV includes all patients irrespective of their condition at the time of diagnosis. It shows that the death rate for endocrine methods was much less six months after treatment was started and after forty-eight months a considerable advanage was still maintained. No comparison of the two endocrine methods seems justified because of the small numbers in the two groups.

TABLE V

From University of Michigan Hospital

COMPARISON OF SURVIVAL PERIOD OF PATIENTS WITHOUT METASTASES

Month	*Control 388 Cases*		*Orchiectomy 45*		*Stilbestrol 33*	
	No. Dead	*% Dead*	*No. Dead*	*% Dead*	*No. Dead*	*% Dead*
6	106	27.3	2	4.4	0	0.
12	168	43.3	6	13.3	2	6.
18	211	54.3	8	17.7	4	12.1
24	233	60.0	14	31.1	5	15.1
30	255	65.7	15	33.3		
36	269	69.2	20	44.4		
42	288	72.6	23	51.1		
48	292	75.2	26	57.7		

TABLE VI

From University of Michigan Hospital

COMPARISON OF SURVIVAL PERIOD OF PATIENTS WITH METASTASES

Month	*Control 260 Cases*		*Orchiectomy 30*		*Stilbestrol 17*	
	No. Dead	*% Dead*	*No. Dead*	*% Dead*	*No. Dead*	*% Dead*
6	97	37.	4	13.3	0	0
12	149	57.	8	26.6	0	0
18	189	73.	12	39.9	6	35.3
24	214	82.	14	46.5	10	58.8
30	227	87.	17	56.5		
36	234	90.	22	73.1		
42	239	91.				
48	240	92.	23	76.4		

Tables V and VI also show increased longevity in patients treated by endocrine methods before and after metastasis has occurred respectively.

Even a brief review such as this shows that many investigators, studying different aspects of the problem during the past few years have added much to our knowledge of prostatic cancers and that as a

result the clinical course of many patients has been improved. Even so, only a beginning has been made. It has long been known that the clinical course of prostatic cancers depends to a great extent on their structure. Experience with endocrine therapy shows that tumor structure also strongly influences response to this form of treatment but, as yet, we are unable to correlate the two. It is also striking how uniform a pattern of end results is seen in each comprehensive group treated by modifying the endocrines but no less striking is the wide variation in the response of individual patients to the same treatment. At present knowledge does not permit individualized treatment for what must be many biologically different prostatic cancers but ignorance compels a repetition of practically the same empirical measures with each succeeding patient. With the realization of such present shortcomings it is gratifying to know that steroid hormone investigations now in progress in the laboratories of the Memorial Hospital promise to reveal clearly the one or more chemical substances which cause the origin and development of prostatic cancers. Furthermore, it is not too fanciful to predict that the time approaches when these guilty substances will be detected in young men and neutralized or destroyed before malignant changes in the prostate have begun.

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RESULTS OF PROSTIGMINE AND TRIDIONE THERAPY IN FIFTY CASES OF SPASTIC NEUROLOGICAL DISORDERS*

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THE effect of prostigmine therapy in several diseases in which muscular paralysis, tension, spasm, and painful cramps are prominent symptoms has been widely publicized during the past four years. Kabat and Knapp,[1] Geyerhahn,[2] Frankel,[3] Fox and Spankus,[4] and others have reported beneficial results with prostigmine in cases of poliomyelitis. They have observed relief from pain, relaxation of muscular spasm, and increase in strength and muscular coördination after treatment in the acute stages with this drug. Trommer and Cohen[5] and Kabat[6] reported good results in cases of chronic rheumatoid arthritis, and ventured the opinion that prostigmine was a far more efficacious drug in the relief of associated muscle spasm than any other drug previously used, including analgesics. Kabat and Jones[7] widened the therapeutic applications for prostigmine by obtaining satisfactory results in the treatment of pain, spasm, and limitation of motion associated with such entities as subacromial bursitis, cervical intramuscular fibrositis, disabilities after fractures, and low back pain. An evaluation of the true therapeutic effect of this drug on muscle spasm per se has been extremely difficult in view of the fact that most series of treated cases have had intensive adjunctive physiotherapy.

It was postulated by Kabat and Knapp,[1] in their original work, that the site of action of prostigmine in cases of muscle spasm was in

* From the Neurological Service of Dr. Foster Kennedy, Bellevue Hosital, (Cornell Division), New York, N. Y. Assistance in the accumulation of data by Dr. Frank Espey, Research Fellow, Neurological Division, is hereby acknowledged.
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the spinal cord on the synaptic connections to the anterior horn cells, and not at the myo-neural junction, where its locus of action has been postulated in myasthenia gravis. Evidence to support this hypothesis has not been conclusive.

It would seem that if prostigmine relieves muscular spasm, caused by such distinctly different diseases as poliomyelitis, arthritis, and local muscular disorders, its usefulness might well be extended to the large number of neurological disorders in which spasticity or rigidity of muscles is an important, and often, disabling clinical feature. Schaubel[8] and Jepson[9] have treated cases of infantile cerebral spastic palsy with prostigmine, and observed encouraging results. (However, isolated instances of spastic neurological disease have been treated by us without obvious or convincing clinical improvement. In these few random cases, improvement followed only the institution of adequate physiotherapy, and seemed to occur independently of the drug therapy). The present study was, therefore, undertaken to give prostigmine therapy an adequate clinical trial in a wide variety of spastic neurological disorders.

In the pharmacological and clinical studies with tridione (3,5,5,-trimethyloxazolidine-2,4-dione) it was observed that, in addition to its anti-convulsant and analgesic properties, this drug had "anti-spastic" effects similar to those previously observed with prostigmine. One investigator[10] reported the use of tridione in 15 cases of cerebral palsies, of which five were of the extrapyramidal type and ten were of the cerebral spastic type; four of the five in the extrapyramidal group and seven of the ten in the cerebral spastic group were reported to show improvement in gait and ability to coördinate movements. In only two of the fifteen cases did the tridione appear to aggravate the condition. Perlstein and Andelman[11] in children with cerebral palsy, reported substantial improvement with tridione therapy, when the condition seemed to be associated with a psychogenic component. It was of little value, however, in relieving the involuntary spasticity or dystonia. Tetanic spasms were controlled by the intravenous administration of tridione. Chorea and postencephalitic Parkinsonism failed to respond in their series.

Since so few data exist as to the effect of tridione therapy on neuromuscular dysfunction, a companion study of the action of tridione on spastic neurological disorders was incorporated in the present investigation.

Material and Method

Fifty cases of various spastic neurological conditions were studied. These fell into the following classification:

A.	Hemiplegias (12):	
	1. Cerebro-vascular occlusions	9
	2. Intracranial neoplasms	2
	3. Cranio-cerebral trauma	1
B.	Paraplegias (9):	
	4. Spinal cord compression	3
	5. Vascular myelopathies	2
	6. Traumatic paraplegias	4
C.	Miscellaneous (pyramidal tract lesions) (13):	
	7. Multiple sclerosis	6
	8. Amyotrophic lateral sclerosis	2
	9. Primary (?) lateral sclerosis	4
	10. Subacute combined sclerosis	1
D.	Extra-pyramidal disorders (16):	
	11. Chronic Parkinsonism	13
	12. Congenital extensor rigidity	1
	13. Extra-pyramidal rigidity, etiology	1
	14. Choreo-athetosis	1
	Total	50

Measurement of the response of muscle spasticity to each medication was formulated with difficulty at first, since it was not possible to use any known goniometer. Limitation of motion, usually measured by this instrument, was not a feature of more than half of the cases. However, with the end-point of obvious objective and subjective improvement in mind, the following simple criteria were conceived:

1. Passive resistance of the involved extremity.
2. Ability to walk without support.
3. Ability to walk a straight line.
4. Degree of adductor lower limb spasm.
5. Slowness of movement.
6. Ability to stand on one leg.
7. Tremor or other involuntary movements.
8. Subjective changes.

The degree of impairment for items 1, 4, 5 and 7 was listed as: 1'—none; 2'—mild; 3'—moderate; and 4'—severe. With associated weakness, ataxia, and involuntary movements varying with the type of neurological disorder, the primary criterion in which we were interested was passive resistance of the extremity. The other criteria depended too much on neurological disabilities other than muscle spasticity. Two other variables which had to be reconciled with the study were physiotherapy and spontaneous improvement. Heat, massage, passive exercise, and other physiotherapeutic procedures were continued during the course of drug therapy in sixteen of the fifty cases (32 per cent). These were distributed approximately equally in the different diagnostic classifications. Comparison with those cases not receiving physiotherapy was, therefore, possible should a noticeable difference in the response of the two groups occur. The well-known chronicity of the vast majority of neurological diseases included in this study diminished the possible error of spontaneous improvement. This factor was almost completely excluded by the over-all results in the series.

Method of Administration: A. Prostigmine*—This drug was given by the combined oral-parenteral route. Prostigmine bromide in doses of 15 mg. t.i.d. was given by mouth during the first three days of therapy, together with subcutaneous injections of Prostigmine methylsulfate, 1 mg. t.i.d. After three days, the oral dose was gradually increased in increments of 15 mg. until the patient was receiving 45 mg. t.i.d. by mouth and the continued 1 mg. injection, t.i.d., by the beginning of the second week of therapy. Atropine sulfate, in doses of 0.2 to 0.6 mg., was given only in those cases having side-effects from prostigmine. The duration of treatment in each case varied from three to six weeks. Shorter than three-week courses were used only in several cases of Parkinsonism, in which cases the drug was discontinued by the patient on his own initiative because of exacerbation of symptoms.

B. Tridione†—The oral preparation of tridione was used in all cases. Doses of 0.3 Gm. t.i.d. were given for one week. This was then increased to 0.6 Gm. t.i.d. for the next two weeks, and in some instances, for as long as the next four weeks. The duration of tridione therapy, therefore, ranged from three to five weeks.

Each of the fifty cases in this series received individual courses of both tridione and prostigmine therapy, although the duration between these courses in the same patient varied considerably: from two weeks to three months. Four types of response to each drug were recorded: 1) *Definite* improvement—if the degree of passive resistance and facility of movement changed 2 degrees or more, e.g.—from severe to mild, or from moderate to none; 2) *Slight* improvement—if the response changed only one degree, e.g.—from moderate to mild; 3) *No* improvement—with its obvious connotations; 4) Aggravation of clinical signs.

Results

Table I illustrates the end-results of therapy with prostigmine. All twelve cases of hemiplegia failed to show improvement in passive resistance during the therapeutic trial. Since this group included nine cases of cerebrovascular lesions, some interesting variations existed. Three of the nine cases had flaccid hemiplegias at the beginning of therapy, having been quite recent vascular occlusions. Drug therapy in these instances was used in an effort to diminish or prevent the muscle spasticity which usually develops within the first two weeks after these occlusions, yet in two cases, muscle spasticity developed as would have normally been expected. In the third, the hemiplegia remained flaccid throughout the patient's hospital stay. Since a certain number of vascular hemiplegias ordinarily remain flaccid, depending on the site and extent of the lesion, this type of study with unpredictable variables, was discontinued.

No instances of definite improvement occurred with prostigmine therapy. Only three cases were recorded as showing slight improvement, one a case of cord compression from adhesive arachnoiditis, an-

* Supplied by Hoffmann-LaRoche, Inc., Nutley, N. J.
† Supplied by Abbott Laboratories, North Chicago, Illinois.

TABLE I

RESULTS OF PROSTIGMINE THERAPY ON MUSCLE SPASTICITY

Case Group	Total #	Degree of Improvement			
		Definite	*Slight*	*None*	*Worse*
A. Hemiplegias	12	0	0	12	0
B. Paraplegias	9	0	1	8	0
C. Miscellaneous	13	0	1	12	0
D. Extra-pyramidal disorders	16	0	1	7	8
Total	50	0	3	39	8

TABLE II

RESULTS OF TRIDIONE THERAPY ON MUSCLE SPASTICITY

Case Group	Total #	Degree of Improvement			
		Definite	*Slight*	*None*	*Worse*
A. Hemiplegias	12	0	1	11	0
B. Paraplegias	9	0	0	9	0
C. Miscellaneous	13	2	2	9	0
D. Extra-pyramidal disorders	16	0	0	5	11
Total	50	2	3	34	11

other a case of so-called primary lateral sclerosis, and the third an unusual type of extrapyramidal syndrome, either congenital or post-encephalitic in origin, and manifested chiefly by marked increase in extensor tonus of the lower extremities causing severe equino-varus deformities of the feet.

Of the 13 cases of chronic Parkinsonism (which included paralysis agitans, arteriosclerotics, and post-encephalitics), it was noteworthy that eight had severe aggravation of their symptoms: "stiffness". This required self-withdrawal of the drug. In half of these cases, the increase in severity of symptoms started during the five-day trial period after the cessation of all previous therapy, and was not relieved by prostigmine. In the other four cases, exacerbation of symptoms occurred during the course of prostigmine therapy.

The results of tridione therapy (Table II) were no more striking, but did include two cases, one of amyotrophic lateral sclerosis and another of primary lateral sclerosis, which clearly showed definite improvement during the four-week course of therapy (see Table II). Three other cases (hemiplegia from vascular accident, multiple sclerosis, and primary lateral sclerosis) showed slight improvement. The remaining 45 cases had either no clinical improvement in muscle tonus, or were decidedly worse during treatment. This latter group again included only cases of chronic Parkinsonism, eleven of which had to discontinue therapy on their own accord.

Complications were minor during each of the drug therapies. The gastrointestinal complaints associated with prostigmine therapy were easily controlled by judicious use of atropine. Four types of complications followed tridione therapy. Visual complaints (photophobia or hemeralopia) occurred in 50 per cent of the series. Marked leukopenia was not encountered in a single instance, although 18 cases (35 per cent) had significantly lower leukocyte counts at the completion of therapy, as compared to the pre-treatment counts. It must be remembered that the courses of tridione therapy were relatively short in this series, when compared with the use of tridione in the epilepsies. More pronounced decreases in leukocyte counts were, therefore, not expected. One patient presented the unusual complication of singultus which disappeared when therapy was stopped, recurred once when tridione was repeated, but did not recur on a third trial. During the third trial, however, an erythematous maculo-papular eruption developed over the patient's face and chest. One other patient had an episode of severe gastrointestinal complaints consisting of abdominal cramps and nausea, both of which disappeared within 24 hours after withdrawal of the drug.

Conclusions

Neither prostigmine nor tridione produced any significant therapeutic effect on muscle spasticity in fifty cases of various neurological disorders, with the common manifestation of demonstrable increase in muscle tonus. This lack of improvement is in sharp contrast to the reported benefits from prostigmine on muscle spasm associated with poliomyelitis, extremity fractures, rheumatoid arthritis, fibrositis, etc., and does not compare favorably with the results of prostigmine or

tridione therapy reported by some investigators in the management of infantile cerebral spastic palsy.

An explanation may be offered for this discrepancy of results. It is possible that the proposed hypothesis for the central action of prostigmine in cases of muscle spasm is in error, and that the drug acts in the usual manner at the neuromuscular junction, relieving spasm only when it is the result of increased muscle irritability on the basis of local inflammatory processes or reflex spasm from involvement of anterior horn cells. This type of action may not, therefore, be expected to relieve spasticity based on destruction of pyramidal or extra-pyramidal tracts in the central nervous system. There is the additional possibility that previous favorable reports of the action of prostigmine on diseases with muscle spasm reflect more the results of concomitant physiotherapy than of the drug action itself.

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CLINICAL MANIFESTATIONS OF ADRENAL CORTICAL HYPERFUNCTION*

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DURING the past two decades many aspects of the functions of the adrenal cortex have been elaborated and clarified. In great part our understanding of the physiology of the adrenals has been the result of experimental observations associated with the removal of the adrenal glands. In this way we learned about the effects of the adrenal cortex on electrolyte and carbohydrate metabolism, on renal function, on growth of young animals, on resistance to stress, its relation to blood pressure and muscular response. In a sense, then, our knowledge has been achieved in a negative way in terms of things that happen to the body when it is deprived of adrenal cortical secretions.

With the isolation of active adrenal cortical hormonal fractions attempts were made to determine the effects of hyperfunction of the adrenal cortex on the body economy. These observations were only in part satisfactory. We know that the injection of certain of the steroid cortical fractions results in the retention of blood sodium and water, an increase in blood pressure, alterations in carbohydrate metabolism. but we have not succeeded in duplicating the clinical picture which we commonly associate with hyperfunction of the adrenal cortex. The basic blood chemical findings, the asthenia, the hypotension, the gastrointestinal symptoms, and the fatal termination of the bilaterally adrenalectomized animal are not dissimilar to the clinical picture observed in patients with Addison's disease. But the clinical adrenogenital syndrome cannot be duplicated by the injection of the available cortical hormones into the experimental animal. There are probably several reasons for this. The hormonal fractions that we have available are probably by no means the only ones elaborated by the adrenal. The system of endocrine balance operative in the normal individual or in the normal experimental animal is in all probability not affected by

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injections of cortical hormones in the same fashion as in the adrenogenital syndrome in the human where the adrenals or the pituitary are the seat of overt disease. It does not follow, however, that because we fail to duplicate the adrenogenital syndrome in the experimental animal with our available techniques that such a syndrome is not due to disease of the adrenal cortex.

Our studies then, concerning the role of hyperfunction of the adrenal cortex are dependent upon clinical observations in patients with demonstrable disease of these glands. The most outstanding clinical entity in this respect is the adrenogenital syndrome. Here too the observations are by no means clear cut. Although patients with an adrenal cortical tumor will manifest a certain clinical picture, similar if not identical observations are elicited in patients who have pathology elsewhere than in the adrenal. We attempt to explain this phenomenon in part at least by the influence of the other glands on adrenal cortical function and vice versa. There has been a good deal of speculation concerning the role of the adrenal cortex in the production of certain isolated clinical phenomena, such as hirsutism, perhaps hypertension, obesity, and menstrual abnormalities, but the evidence of such a relationship is not an entirely convincing one. We must, therefore, use the adrenogenital syndrome due to a tumor of the adrenal cortex or to hyperplasia of the adrenal cortex as the starting point from which to study the clinical role of adrenal cortical hyperfunction.

In a general way we may divide the symptoms of the adrenogenital syndrome into three large groups: 1) Those associated with premature sexual and physical development; 2) Those associated with signs and manifestations of increased or decreased virility; and 3) Those other symptoms which are part of the disease but are not manifestations or disturbances in sexual physiology. The first group includes the evidences of pseudohermaphroditism and precocious physical development. In the second category are the manifestation of male virilism in the female, and in the male signs of feminization. The third group includes the development of obesity, hypertension, glycosuria, osteoporosis, purplish striae, polycythemia, dusky cyanotic discoloration of the skin, acneform eruptions, and a tendency to purpura and ecchymosis. In a strict, legalistic sense the symptoms of the first two groups are referred to as the adrenogenital syndrome, while those of the third group are known as the Cushing's syndrome.

The clinical picture which patients with adrenal cortical hyperfunction will manifest is dependent in great part on the age at which such cortical abnormality occurs, and in part on the sex of the patient. In addition, however, there would seem to be no clear cut explanation at the present time as to why some patients will show predominantly the picture of an adrenogenital syndrome, while in others the major manifestations are those of the curious metabolic disturbances referred to as Cushing's syndrome. and a third group will show a combination of both. Histologically the tumor or hyperplasia found in one group is not distinguishable from that found in the other. But we must assume that not all of the adrenal cortical cells are hormone secreting cells, nor that all the cells secrete the same hormones at the same time. It is theoretically possible, therefore, that the different clinical manifestations are also due in some part to the different adrenal cortical cells with their different functions which may be involved.

It is worth emphasizing again that an identical picture may be produced by a tumor of the adrenal cortex, bilateral hyperplasia of the adrenal cortex, or in the presence of an ostensibly normal adrenal cortex associated with a tumor of the anterior lobe of the hypophysis. These pituitary tumors are usually basophil in character, but very occasionally they are made up of sarcomatous or undifferentiated cells. Finally, to add to our confusion, an identical clinical picture may be presented in the absence of any overt anatomical abnormalities associated with any of the endocrine glands. However, one consistent histological abnormality has been observed in the vast majority of patients with the adrenogenital-Cushing's syndrome. This is the curious hyaline changes in the basophil cells of the anterior lobe of the hypophysis so carefully observed by Crooke[1] and subsequently confirmed by many other investigators. The significance of these changes is by no means clear. Severinghaus and Thompson[2] succeeded in inducing vacuolar and hyaline changes in the basophil cells in the pituitary of the dog indistinguishable from those observed by Crooke in Cushing's syndrome. These changes were induced in one set of animals by the injection of crude sheep anterior pituitary extract over a prolonged period of time, and in another set of dogs by the injection of suitable anti-hormone serum. These authors concluded that the basophilic vacuolation is a characteristic retrogressive phenomenon which the cells undergo when their normal physiology is disturbed and the Crooke changes are re-

garded as an aspect of the general granule liquefaction which also appears after experimental thyroidectomy and after castration.

In the light of the clinical and experimental studies available it is difficult to believe that the cause of the adrenogenital-Cushing's syndrome is these Crooke changes. Rather it is a reasonable assumption that these changes are secondary to the disturbed adrenal cortical function and fall essentially into the same category as the other clinical signs and symptoms, such as hypertension, osteoporosis, and so forth. Similarly one is not impressed with the fundamental causative significance of the fuchsinophilic granules demonstrated in the cells of the adrenal cortex by Broster and Vines.[3] This staining reaction has been observed by Cahill and his coworkers[4] not only in patients wth adrenal cortical tumors but in the adrenals of dogs and individuals without any manifestations of adrenal cortical disease.

What can we conclude, therefore, concerning the etiology of the adrenogenital-Cushing's syndrome? The frequency with which this disease is associated with some overt pathology in the adrenal cortex and the complete reversal of the clinical picture after successful surgical treatment of such adrenal pathology leads one inevitably to the conclusion that these glands play a vital role in the pathogenesis of this syndrome. Even in those instances in which the major pathology is located in the pituitary or hypothalamus the effect of such pathology in the production of the typical clinical picture is probably mediated through the adrenal cortex.[5] The question of the clinical manifestations is in part dependent upon the time of onset of the adrenal cortical disease and in part on the sex of the patient. When hyperplasia or tumor of the adrenal cortex develops in utero pseudohermaphroditism will result. Pseudohermaphroditism is characterized by the presence of the gonads of only one sex, but associated with this are such abnormalities of the external genitalia as to render the identification of the sex through external examination doubtful. Male pseudohermaphrodites are those individuals whose gonads are testes, while female pseudohermaphrodites have ovaries. The classification into male and female pseudohermaphrodites is entirely independent of the nature of the external genitalia, and frequently final determination of the sex requires surgical inspection of the pelvic organs. True hermaphroditism differs from pseudohermaphroditism in that the former is characterized by the presence of the gonads of both sexes in the same person. True hermaphroditism is an embryo-

logical developmental defect and is in no way related to abnormalities of the adrenal cortex.

Marchand[6] was perhaps the first investigator to point out the association of pseudohermaphroditism with hyperplasia of the adrenal cortex. This observation was subsequently confirmed by Glynn,[7] and today we recognize that female pseudohermaphroditism is usually due to hyperplasia of the adrenal cortex occurring in utero and occasionally to adrenal cortical tumor. The pseudohermaphrodite does not present any other manifestations of the Cushing's syndrome, and pseudohermaphroditism is compatible with a long life span.

The development of an adrenal cortical tumor or hyperplasia in children before puberty may result in the production of precocious obesity, excessive muscular development, and marked sexual alterations. It was originally thought that the metabolic disturbances characteristic of Cushing's syndrome were rare in children with adrenal cortical disease. However, this is not so, and we now recognize evidences of this abnormality in these patients.[5] The adrenogenital syndrome in female children is characterized by sexual precocity, the development of hirsutism of the face and limbs, enlargement of the external genitalia, and deepening of the voice. In most instances there is a temporary period of rapid growth which is, however, followed by an early closure of the epiphyses, so that the end result is usually a rather short individual. Menstruation as a rule does not occur even in older children who may have reached the age of puberty, although several notable exceptions have been reported.[5] In general in both boys and girls the clinical picture is that of a rapidly aging process in which during the space of a few short months or years the child develops physically into an adult.

Such adrenal cortical disease in boys is characterized by obesity, marked muscular development, or both. The male children grow rapidly and develop signs of virilism with excessive hirsutism of the face, pubis, and frequently the rest of the body. There is marked precocious sexual development which. unlike that observed in girls, is homologous. The size of the genitals may assume adult proportions, although genital maturation is not necessarily associated with adult potency. However, spermatogenesis has been known to occur, and in at least one reported instance a boy of eight actually acquired a venereal infection through the usual channels.[5]

The development of this syndrome in children is more commonly associated with an adrenal cortical tumor than with adrenal cortical hyperplasia.

The clinical picture in adults is somewhat different from that observed in children. Women afflicted with the disease may manifest predominantly the adrenogenital syndrome, the Cushing's syndrome, or a combination of both. The latter is the most common clinical picture observed. The syndrome is seen more commonly in women than in men and may occur at any age between puberty and the menopause. Most instances are observed between the second and fourth decades of life, although some cases occurring after the menopause have been reported.[5]

The adrenogenital syndrome in women is characterized by virilism with the appearance of secondary male characteristics and the suppression of at least many of the female characteristics. They develop extensive hirsutism of the face, often with a well defined moustache and beard requiring daily shaving. There is usually an increase of hair over the extremities and over the pubis, the latter acquiring a male pattern. The hair may be fine and silky in character, or it may be long, coarse, and thick. Either directly before or coincidental with the hypertrichosis there occurs an alteration in the menses. They become scanty and infrequent and eventually cease entirely. Associated with this there occurs a diminution in libido and occasionally even a transfer of sexual interest to other females. There follows atrophy of the breasts and a decrease in chest and hip fat. Muscular development becomes more pronounced and the entire physical configuration tends to assume the male form. The clitoris may hypertrophy, and labia darken somewhat in color, and the uterus and adnexae tend to shrink somewhat in size. The voice deepens and becomes rough, probably due to thickening and elongation of the vocal cords. When there are associated evidences of Cushing's syndrome these patients will manifest. in addition to the virilism, hypertension,[8] a curiously distributed obesity, osteoporosis, moonlike facies, alterations in carbohydrate metabolism, purplish striae, and so forth. Occasionally the only evidence of adrenal cortical disease may be a very marked obesity.

Hormonal adrenal cortical tumors or adrenal cortical hyperplasia in the male are extremely rare. When they occur they generally assume one of two forms. Either they present the picture of Cushing's syndrome without virilism but with some loss of libido and a decrease in

size of the genitals, or they show actual signs of marked feminization with comparatively few manifestations of the Cushing's counterpart. Where feminization in the male has been very marked the pathology has generally proven to be an adrenal cortical carcinoma. In adult males, in contrast to prepuberal boys, the sexual abnormalities are characterized not by an increase in virilism but rather by the development of feminine characteristics.

In this general discussion concerning the symptoms of adrenal cortical tumors we have placed great emphasis upon the distinction between the sexual abnormalities observed and the metabolic aberrations characteristic of the Cushing's syndrome. This distinction is of considerable practical significance. The life span of the patient who shows virilism alone is considerably longer and the outlook very much better than is the case with the patient who shows evidence of Cushing's syndrome. In the latter group the contralateral adrenal is always atrophic, either grossly or functionally, and the operative risk associated with removal of the adrenal tumor is exorbitantly high. This is particularly true of the benign hormonal adrenal cortical tumors, in contrast to the malignant ones. The malignant tumors can often be removed with comparatively small operative fatality, probably because metastases occur early. These metastases constitute functioning adrenal cortical tissue.[5] On the other hand, in our experience, and this I think is fairly uniform with some modifications, the operative mortality following the removal of a benign hormonal adrenal cortical tumor in patients with Cushing's syndrome is excessively high. In patients who present only virilism the contralateral adrenal is perfectly normal, and the removal of the tumor can be effected without any undue operative fatality. Where hyperplasia of the adrenal cortex is the cause of the syndrome such hyperplasia is bilateral and one adrenal can always be removed quite safely.

In view of the relationship of the adrenal cortex to electrolyte metabolism one would expect that this would be reflected in some fashion in patients with adrenal cortical hyperfunction. Since in adrenal cortical deprivation there occurs a reduction in the serum sodium and chloride with an increase in the serum potassium, it would seem that in hyperfunction of the adrenal cortex the direct antithesis of this might be observed. It is of great interest that such electrolyte changes are relatively infrequently seen in patients with the adrenogenital-Cushing's syndrome. Of forty-five well defined instances of this syndrome

TABLE I

FORTY-FIVE COLLECTED CASES FROM THE LITERATURE IN WHICH BLOOD ELECTROLYTE LEVELS WERE RECORDED

	Normal	*Elevated*	*Reduced*	*Questionable Elevation*	*Questionable Reduction*
Na	38	4	0	3	..
Cl	40	0	5	..	..
K	33	0	8	..	..

collected from the literature, in which adequate blood sodium, chloride, and potassium levels were determined, some abnormalities in the sodium ion values were found in seven instances, in chloride levels in five, and in potassium values in eleven instances. Where abnormality of the blood sodium has been evident, it has usually been characterized by an increase in this ion. The chlorides and potassium, on the other hand, if abnormal have usually shown a decrease in serum concentration. Kepler[9] reported the occurrence of a reduction in the blood level of chlorides and potassium, a considerable elevation in the blood CO_2. and a normal concentration of blood sodium. McQuarrie and his group[10] also demonstrated considerable alkalosis, reduction in the blood chlorides and potassium. but in addition in his patient there was a marked elevation in the blood sodium level.

It will be noted that in those instances in which electrolyte changes occurred any one of a number of variations was possible, but in most cases the striking changes were the reduction in the blood levels of potassium and chloride with an alkalosis and with or without elevation of the blood sodium. The alkalosis and the low blood chlorides were in no instances due to vomiting but rather were in some way associated with the disturbance of potassium metabolism. Willson and his coworkers[11] found, on the basis of careful metabolic studies that the reduction in plasma potassium mirrored a marked depletion of the intracellular potassium stores. These authors felt that this depletion in body potassium probably conditioned the chloride level, since the addition of potassium citrate to the diet resulted in an increase in the plasma concentration of both potassium and chlorides. On the other hand, the administration of ammonium chloride alone failed to affect the blood chloride level.

It is not surprising that patients with adrenal cortical hyperfunction should manifest alterations in the blood electrolyte levels. Anderson and Haymaker[12, 13] demonstrated that extracts of the blood and urine of such patients were capable of prolonging the lives of adrenalectomized rats beyond the survival of untreated controls. The salt retaining effect of 1 cc. of blood was found to be equivalent to 4 to 6 grams of fresh adrenal tissue. It is astonishing, however, that such ion abnormalities are relatively infrequently observed, and it suggests the existence of some compensatory mechanism which controls the amount of salt retaining hormone manufactured under these circumstances. Some clue to the nature of this control was elicited in studies conducted in our laboratory.[5] We observed that in normal individuals the intravenous injection of salt following the intramuscular injection of a single dose of desoxycorticosterone acetate resulted in a considerable retention of injected salt above that seen prior to the injection of the hormone. In contrast to this result, the patients with Cushing's syndrome showed a pronounced sodium chloride diuresis. The evidence would suggest that the excessive salt retaining hormone formed is rapidly converted into another substance lacking salt retaining effects. In view of the close chemical similarity between desoxycorticosterone and other adrenal steroid hormones which have no salt retaining effect, the conversion of the former into the latter would seem entirely feasible. It might be anticipated that this compensatory mechanism is not entirely effective in those individuals who manifest a disturbance in the blood electrolyte pattern. This is borne out by our observations in two cases of adrenal cortical tumors in which there was a considerable elevation of the plasma sodium. In both instances the injection of desoxycorticosterone under the conditions of our experiment failed to produce a sodium chloride diuresis.

The lack of abnormalities in the blood electrolyte pattern cannot be used as a point in differential diagnosis in adrenal cortical hyperfunction. The presence of the characteristic blood electrolyte disturbance is strongly suggestive of adrenal cortical hyperfunction. Its absence, however, does not rule out such a diagnosis.

Within recent years considerable time has been devoted to the investigation of hormonal products produced by the adrenal cortex, and attempts have been made to determine both the total amount of such compounds as well as the individual fractions in the urine of normal

TABLE II

ANDROGENIC AND ESTROGENIC COMPOUNDS
ISOLATED FROM THE ADRENAL CORTEX

Adrenosterone
11-hydroxyisoandrosterone
17-hydroxy-progesterone
Theelin

ANDROGENIC, ESTROGENIC, AND INERT COMPOUNDS
ISOLATED FROM NORMAL URINE OF MEN AND WOMEN

Androsterone
Dehydroisoandrosterone
3-α-hydroxyethicolane-17-one
Pregnanediol
Estrogens

ANDROGENIC, ESTROGENIC, AND INERT COMPOUNDS ISOLATED FROM THE URINE OF MEN AND WOMEN WITH HYPERFUNCTION OF THE ADRENAL CORTEX

(Tumors, Hyperplasia, Basophilism)

Androsterone
Dehydroisoandrosterone
3-α-hydroxyetiocholane-17-one
Pregnanediol
Estrogens
$\Delta_{3,5,}$-androstadiene-17-one
Isoandrosterone
Pregnane-3, 17, 20-triol
3-α-hydroxyandrosten-17-one

individuals and in patients with adrenal cortical hyperfunction. Normal men and women excrete both androgenic and estrogenic compounds in the urine. These compounds, however. have their origin not only in the gonads but also in the adrenal cortices. In addition to the physiologically active compounds which are excreted in the urine and which have their origin in the adrenals, inert compounds, probably degradation products of the active substances elaborated in the adrenal cortex, are also found in the urine. Some of these compounds are present in the urines of normal men and women, while other substances exist only in pathological states associated with hyperfunction of the adrenal cortex. It is of considerable interest that the actual androgenic content of

hyperplastic or neoplastic adrenals is extremely low despite the fact that they may give rise to excessive amounts of androgenic substances in the urine. This would suggest that only minute amounts of such substances are stored in the gland where they are manufactured. In the adjoined table are listed those hormones which have been isolated and identified from the adrenal cortex, from the urine of normal men and women, and from the urine of men and women with adrenal cortical hyperfunction. Of the androgenic compounds isolated from the adrenal cortex all have androgenic activity although to varying degrees; 17-hydroxy-progesterone is about as androgenic as androsterone, while adrenosterone has an androgenic activity one-fifth of androsterone, and 11-hydroxyisoandrosterone has an androgenic activity equal to approximately one-thirtieth of androsterone. Of the androgenic compounds isolated in the urine of normals and patients with adrenal cortical hyperfunction androsterone, dehydroisoandrosterone, $\Delta_{3,5}$androstadiene-17-one, and isoandrosterone are known to have definite androgenic activity. 3-α-hydroxyetiocholane-17-one is physiologically inert. The pregnane triols probably lack androgenic activity if one is to judge by their chemical structure. Only a limited number of androgenic and inert degradation products are found in the urine of normal men and women, while several additional compounds are excreted in the urine of patients with adrenal cortical hyperfunction. We have identified by no means all of these latter compounds, and with improvements in chemical techniques it is not unlikely that many more such compounds will be isolated and identified.

In the routine laboratory diagnosis of adrenal cortical hyperfunction it is obviously impossible to attempt to isolate the various androgenic and inert fractions from the urine. Attempts are, therefore, made to determine the total androgenic and estrogenic activity of the urine specimen without identifying individual constituents. For this purpose, androgenic activity is measured by the "capon comb growth" technique, and estrogenic activity in spayed adult rats according to the vaginal spread technique of D'Amour and Gustavson.[14] In general, there is a marked variation in the urinary excretion of both androgens and estrogens, and the clinical significance of one or two twenty-four hour urine assays must not be unduly emphasized. In hyperfunction of the adrenal cortex there is a surprising lack of correlation between the clinical picture and the urinary sex hormone assays. In general it may

TABLE III

ANDROGEN AND ESTROGEN URINARY EXCRETION IN HYPERFUNCTION OF THE ADRENAL CORTEX

Diagnosis	*Daily excretion of urinary androgens*	*Daily excretion of urinary estrogens*
Carcinoma of adrenal cortex	May be excessive	May be excessive
Benign tumors of adrenal cortex	Usually normal. May be slightly to moderately increased	Usually normal. May be slightly to moderately increased
Hyperplasia of adrenal cortex	Usually normal. May be slightly to moderately increased	Usually normal. May be slightly to moderately increased
Pituitary basophilism	Usually normal. May be slightly to moderately increased	Usually normal. May be slightly to moderately increased

be said that in carcinoma of the adrenal cortex there may be an excessive daily urinary excretion of either androgens or estrogens or both, while in benign tumors of the adrenal cortex, in hyperplasia of the adrenal cortex, and in pituitary basophilism the excretion of these urinary androgens and estrogens is frequently normal and only occasionally somewhat increased. These techniques, then, leave a good deal to be desired, both because they are rather complicated and because they yield rather meager information. It should be emphasized again that the biological determination of urinary androgens and estrogens is specific for neither one substance nor for the steroids originating from a single gland. What we are determining, in effect, are those steroids originating from the gonads and the adrenals which exercise definite androgenic or estrogenic activity. The biological assay, then, has the disadvantage of not including those steroid compounds present in the urine, and under certain circumstances in abnormal quantities, which manifest neither androgenic nor estrogenic activity. The urinary excretion of such inert compounds may be considerably increased in disease of the adrenal cortex and yet remain unidentified with the biological techniques. This may perhaps account in part at least for the infrequency with which abnormalities in assay are found to exist in patients with proven adrenal cortical disease.

TABLE IV

URINARY EXCRETION OF 17-KETOSTEROIDS IN HYPERFUNCTION OF ADRENAL CORTEX

	Number of cases	*Normal Amount*	*Slight increase*	*increase Moderate*	*Excessive increase*
Virilism (no overt adrenal pathology)	64	35	24	5	0
Cushing's syndrome (no overt adrenal pathology)	14	10	2	2	0
Virilism with Cushing's syndrome (adrenal cortical hyperplasia)	12	2	1	5	4
Virilism with Cushing's syndrome (adrenal cortical carcinoma)	14	1	0	3	10

There are several advantages to the determination of the urinary 17-ketosteroids over the biological assay for androgens and estrogens. Since the determination of the urinary 17-neutral ketosteroids is a chemical procedure it is generally simpler and less time consuming than the biological assay. In addition, the urinary 17-ketosteroids include not only steroid compounds with androgenic activity but also inert compounds like 3-α-hydroxyetiocholane-17-one. However, this chemical reaction is specifically for the determination of non-phenolic neutral 17-ketosteroids and consequently testosterone, which is an androgen although not a 17-ketosteroid, is not included in the determination. Estrogenic hormone, which is a 17-ketosteroid, is not included in the determination because it is a weak phenol and is removed by the washing with alkali which is a step in the extraction process. These, then, are the disadvantages of the biochemical test for the determination of 17-ketosteroids. This method is actually not a test for androgens, although it may parallel the latter.

The normal values for the urinary excretion of 17-neutral ketosteroids vary with the age and with the sex. In general the values are lower in children than in adults, and lower in women than in men. The high value obtained in males is dependent upon the fact that these compounds are elaborated by the adrenals and by the male gonads. In our experi-

ence the twenty-four hour urinary excretion of the 17-neutral ketosteroids in women varies from approximately 5 to 15 mgm. with an average value of about 10 to 12, while in the male it varies from 8 to 18 mgm. in twenty-four hours with an average value of 15 mgm.

In Table IV are the results obtained of the urinary excretion of 17-ketosteroids in hyperfunction of the adrenal cortex. In this table it is seen that the largest excretions occur in instances of adrenal cortical carcinoma, while in patients with adrenal cortical hyperplasia there is frequently a considerable increase. In patients with virilism alone in whom there is no overt adrenal pathology, or in patients with Cushing's syndrome in whom the pathology is located mostly in the pituitary, the urinary excretion of 17-neutral ketosteroids is frequently normal and not infrequently shows only a slight to moderate increase. One cannot, therefore, draw any definite conclusions as to the diagnosis from the determination of the urinary 17-ketosteroids alone. In general, one may say that the absence of any excessive excretion is a point against, but by no means excludes, the diagnosis of an adrenal cortical carcinoma.

The diagnosis of adrenal cortical hyperfunction is therefore made on the basis of a number of factors rather than on one isolated manifestation. The factors which should be emphasized are the typical clinical history, the characteristic physical appearance, changes in the blood electrolytes, if present, and determination of the 17-neutral ketosteroids. Intravenous pyelography may help in determining the possibility of an adrenal tumor. Of even greater aid is perirenal insufflation which may show the presence of an adrenal cortical tumor or hyperplasia.

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